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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS

Ex parte **DING et al.**
Appeal No. ____________

Serial No.:	09/268,437
Filed:	March 12, 1999
Applicant:	Ying Ding, Brian Halsall and William R. Heineman
Title:	**SIMULTANEOUS MULTIANALYTE ELECTROCHEMICAL ASSAY BASED ON SPATIAL RESOLUTION**
Art Unit:	1641
Examiner:	Gail R. Gabel

APPEAL BRIEF

Transmitted herewith, in triplicate, is the APPEAL BRIEF in this application, with respect to the Notice of Appeal filed on February 19, 2003.

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

In re Application of:	**DING et al.**
Serial Number:	09/268,437
Filed:	March 12, 1999
Art Unit:	1641
Examiner:	Gailene R. Gabel
Appellants:	Ying Ding, Brian Halsall and William R. Heineman
Title:	**SIMULTANEOUS MULTIANALYTE ELECTROCHEMICAL ASSAY BASED ON SPATIAL RESOLUTION**
Attorney Docket:	UOC-134A

Hon. Commissioner of Patents and Trademarks
Washington, D.C. 20231

Sir:

APPEAL BRIEF

REAL PARTY IN INTEREST

The subject application is assigned to The University of Cincinnati, of Cincinnati, Ohio.

RELATED APPEALS AND INTERFERENCES

There are no other appeals or interferences related to the application that is the subject of this appeal.

STATUS OF CLAIMS

On February 19, 2003, appellants appealed from the final rejection of claims 1-5 and 10, claims 6-9 having been withdrawn from consideration. Claim 10 has since been canceled by appellants in an Amendment filed concurrently with the Notice of Appeal. This was done in order to reduce the issues on appeal.

Therefore, claims 1-5 remain pending and are involved in this appeal.

STATUS OF AMENDMENTS

An advisory action dated January 17, 2003 stated that proposed minor amendments to claims 1 and 10, filed by appellants on December 19, 2002 in response to the final rejection, were not entered for purposes of Appeal. Claim 10 was canceled in an Amendment filed concurrently with the Notice of Appeal in order to reduce the issues on appeal.

SUMMARY OF INVENTION

This invention relates a simultaneous electrochemical assay device comprising a cell adapted to hold a sample and a plurality of working electrodes adapted to quantitatively measure enzymatic reaction product.

The goal of the invention is to detect multiple analytes in a single sample via analyte binding areas situated at distinct, separate locations, a quiescent solution, and a plurality of working electrodes located within proximity of those distinct, separate locations (page 3, lines 6-10). The assay detects labeled enzymatic reaction product that are either electroactive or catalyze the production of an electroactive product (page 2, lines 5-6).

The invention requires placement of each working electrode adjacent to one analyte binding area, with each working electrode measuring the presence of a certain analyte and being separated from the nearest adjacent analyte binding area by a predetermined distance (page 5, lines 1-9). Since the working electrode for each binding area is spatially separated from adjacent binding areas, a measurement can be taken before cross-interference is created by diffusion of reaction product from an adjacent analyte binding area (page 12, lines 13-16; page 13, lines 3-7).

The predetermined distance between adjacent analyte binding areas is estimated by using the Einstein equation (page 5, lines 9-17). This distance is the minimum distance necessary to prevent

cross-interference between the electrode measuring one type of analyte and the electrode at a second analyte binding site (page 12, lines 5-16). The calculation of this predetermined distance is based upon the physical phenomenon of Fickian diffusion (page 5, lines 1-17; page 12, lines 5-16).

Further, the electrodes are placed in close proximity to their respective analyte binding areas in order to detect actual enzyme reaction product, i.e. the electrodes do more than merely detect electrochemiluminescence (ECL) created by a reporter agent (see page 5, lines 1-9, and page 3, lines 10-15). Indeed, quantitative measurement of enzyme reaction product by the working electrodes is one reason why an individual working electrode must be separated from an adjacent analyte binding area by a predetermined distance. That is, the reaction product from the enzyme at a first analyte binding site will not diffuse in sufficient quantity to interfere with the working electrode at an adjacent analyte binding site (see page 5, lines 4-9). Therefore, the predetermined distance between analyte binding areas is a distance which is effective to permit each electrode to measure the analyte bound to its adjacent analyte binding site, yet prevent that electrode from inadvertently measuring an interfering amount of analyte bound to the nearest adjacent analyte binding site.

The assay device of this invention is applicable to any electrochemical technique which utilizes an electrode, including chronoamperometry, cyclic voltammetry, linear scan voltammetry, pulse voltammetry, and differential pulse voltammetry (see page 9, lines 1-11). The diameter of the electrodes, the width of the antibody immobilization strips, and the distances between detection electrodes are preferably on the "millimeter" scale. However, the scale can be extended to the "micrometer" scale for the above stated dimensions, and is also extendable down to the "nanometer" scale using recently developed methodologies for depositing conducting materials with dimensions in this regime (see page 16, lines 3-17).

ISSUES

Appellants submit this brief in the belief that the sole issue to be determined is whether claims 1-5 are unpatentable under 35 U.S.C. §102(e) as being anticipated by Wohlstadter et al. (U.S. Patent No. 6,066,448).

Claims 1-5 were included in a rejection under 35 U.S.C. §112, first paragraph in the final action, but this rejection specifically addressed claim 10 only, which has since been canceled by the appellants. Accordingly, this brief is written on the assumption that the rejection of claims 1-5 under 35 U.S.C. §112, first paragraph is no longer relevant, such that the Examiner would have to state a new rationale for a 35 U.S.C. §112, first paragraph rejection of claims 1-5 in his answer, and that the new rationale would constitute "a new ground of rejection" of those claims within the meaning of 37 CFR §1.193(a)(2).

GROUPING OF CLAIMS

Claims 1-5 stand or fall together and relate to a simultaneous electrochemical assay device comprising a cell adapted to hold a sample and a plurality of working electrodes adapted to quantitatively measure enzymatic reaction product. The reasons why appellants believe this group of claims is patentable are explained below.

ARGUMENT

I. §102(e) rejections of claims 1-5

The Examiner asserted two rationales for rejecting claims 1-5 under 35 U.S.C. §102(e) as anticipated by Wohlstadter et al.: A) that Wohlstadter discloses a structural requirement for a working electrode, with its corresponding analyte binding area, to be separated from adjacent binding areas by a minimal distance; and B) that Wohlstadter discloses the use of electrodes to quantitatively detect

enzyme reaction product, such that light detection via electrochemiluminescence (ECL) is the not the only manner disclosed for determination of the presence of analyte binding. Appellants respectfully respond that these rationales are in error, and that Wohlstadter does not anticipate the present invention, for the following reasons.

A) Wohlstadter does not have a structural requirement for a working electrode, with its corresponding analyte binding area, to be separate from adjacent binding areas by a minimal, predetermined distance.

The Examiner stated the following in the final rejection dated August 27, 2002:

> "Wohlstadter, indeed, define (sic) structural requirements for a working electrode with its analyte binding area, to be commensurately separate in distance, so as to achieve high surface area to solution volume ratios"
>
> (citing column 51, lines 53-67 of the Wohlstadter patent).

Appellants respectfully assert that the text of column 51, lines 53-67 of Wohlstadter refers only to a method by which individual binding domains function and not to a structural requirement for separating electrodes. More specifically, column 51, lines 64-65 refer merely to an example of how sheets of individual binding domains with "immobilized enzymes on one or both sides may be stacked to achieve high surface area to solution volume ratios." This discloses only that individual binding domains may be stacked as sheets; it does not disclose a requirement for spacing between adjacent binding domains to prevent cross-interference between working electrodes. There is no reference at all in these lines – indeed, there is no reference in the entire patent – to a structural requirement for a working electrode and its corresponding analyte binding area to be separated from adjacent binding areas by a minimal, predetermined distance.

In contrast to Wohlstadter, the present invention teaches a structural requirement for each working electrode to be "separated from the nearest adjacent analyte binding area by a distance", *in*

addition to placement of "...each working electrode adjacent to one analyte binding area..." (see claim 1, and page 5, lines 1-9). The independent electrode for each binding area is spatially separated from adjacent binding areas so that a measurement can be taken before cross-interference occurs due to diffusion of product from adjacent analyte binding areas (see page 3, lines 14-17). An electrode measuring the presence of a certain analyte is separated from the binding area of differing analytes by a predetermined distance, which is estimated by using the Einstein equation, i.e. the minimum distance allowable between the electrode measuring one type of analyte and a second analyte binding site in order to prevent cross-interference (see page 5, lines 1-9 and page 12, lines 5-16). Further, appellants' invention teaches the use of the principles of Fickian diffusion in order to eliminate cross-interference between different analytes (page 5, lines 9-17).

The goal of the present invention is to detect multiple analytes in a single sample by using analyte binding areas at distinct, separate locations, a quiescent solution, and a plurality of working electrodes located within proximity of those distinct, separate locations (see page 3, lines 6-10). Appellants reiterate that there is no teaching by Wohlstadter of a structural requirement for a working electrode, with its corresponding analyte binding area, to be separated from adjacent binding areas by a minimal distance. One of skill in the art will appreciate that appellants' device detects multiple analytes through a different inventive method than Wohlstadter.

B) Light detection via electrochemiluminescence (ECL) is the only manner disclosed by Wohlstadter for determination of the presence of analyte binding.

The Examiner stated the following in the final rejection dated August 27, 2002:

> "Wohlstadter, indeed, teaches quantitatively detecting enzyme product in column 22, lines 24-39, wherein the substrate is the analyte of interest and the product of the enzymatic reaction upon the substrate is a reporter agent (detectable agent)."

Appellants respectfully assert that column 22, lines 24-39 of Wohlstadter does not teach the quantitative measurement of enzyme product, but rather it teaches the measurement of a "reporter agent" *in place of* the actual analyte of interest, i.e. enzyme product. Further, as column 22, lines 27-30 state, the "reporter agent" is, "e.g., a product that triggers an ECL reaction, a fluorescent molecule, a substance that changes color upon contact with appropriate enzyme, etc." There is no teaching by Wohlstadter of the use of electrodes to directly detect the quantitative amount enzyme reaction product. Wohlstadter uses electrodes that are designed to create ECL, and that ECL is then detected photometrically. The electrodes themselves are not adapted to measure reaction product (column 10, lines 7-26). Also, the luminescent material is adjacent to the enzyme which is also bound (column 22, lines 34-39).

Claim 1of the present application clarifies this difference by the phrase "...a plurality of working electrodes adapted to *quantitatively measure enzymatic reaction product...*" (emphasis added). Indeed, quantitative measurement of enzyme reaction product by the working electrodes is one reason why a working electrode must be separated from an adjacent analyte binding area by a distance, so that "the reaction product from the enzyme ... will not diffuse in sufficient quantity to interfere with the first working electrode" (see page 5 lines 1-9, and page 3, lines10-15). Further, the present invention teaches that the electrodes are placed in close proximity to the analyte binding areas in order to directly detect enzymatic reaction product (page 3, lines 6-14; page 5, lines 1-9). Wohlstadter does not teach quantitative measurement of enzyme reaction product by working electrodes. Rather, Wohlstadter places the electrodes in close proximity to the binding areas merely to induce ECL (see column 1, line 56 to column 2, line 12).

Moreover, while Wohlstadter's assay device is limited to ECL alone, the present invention is applicable to any electrochemical technique which utilizes an electrode, including chronoamperometry, cyclic voltammetry, linear scan voltammetry, pulse voltammetry, and differential pulse voltammetry (see page 9, lines1-11). Regarding the size of electrodes possible for the assay, Wohlstadter's electrodes must be large enough to be recorded by a light detector means, preferably on the sub-centimeter size (see column 9, lines 3-15). In contrast, the present invention teaches that the dimensions are in the "millimeter" scale in terms of the diameters of the electrodes, the width of the antibody immobilization strips and the distances between detection electrodes. This concept also extends to the "micrometer" scale for the above stated dimensions, and the present invention teaches that the concept is also extendable down into the "nanometer" scale, using recently developed methodologies for depositing conducting materials with dimensions in this regime (see page 16, lines 3-17).

In light of the foregoing, appellants respectfully assert that Wohlstadter does not attempt to accomplish multiple analyte determination using a system comparable to the present invention. Wohlstadter does not teach the structural requirement of a minimal distance of separation between a working electrode of one analyte binding area and adjacent analyte binding areas to prevent cross-interference, and also does not teach quantitative measurement of enzyme reaction product by the working electrodes. Therefore, one skilled in the art would clearly recognize that the present invention is accomplishing a completely different function with its structure, relative to the device disclosed in Wohlstadter. For these reasons, appellants respectfully assert that claims 1-5 are unpatentable under 35 U.S.C. §102(e).

CONCLUSION

Based on the above argument, it is respectfully submitted that the final rejection of the claims should be reversed or vacated. A check for the fee of $320.00 is attached hereto. If any other charges or credits are necessary to complete this communication, please apply them to Deposit Account 23-3000.

Respectfully submitted,

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APPENDIX

Claims Involved in the Appeal

1. (Thrice Amended) A simultaneous electrochemical assay device comprising a cell adapted to hold a sample, said cell having a surface having a plurality of analyte binding areas, each of said analyte binding areas having a different specific analyte binding substrate; and a plurality of working electrodes adapted to quantitatively measure enzymatic reaction product, each working electrode adjacent to one analyte binding area and separated from the nearest adjacent analyte binding area by a distance wherein said device does not have means to mix a sample in said cell.

2. (Amended) The device claimed in claim 1 wherein said binding substrates comprise a plurality of different analyte specific proteins.

3. (Amended) The device claimed in claim 1 wherein said binding substrates each comprise a different antigen.

4. (Amended) The device claimed in claim 1 wherein said binding substrates comprise a different antibody.

5. (Amended) The device claimed in claim 1 further comprising at least one auxiliary electrode in said cell.